H., Reichardt, L.F., Ryan, A.M., Carver-Moore, K., and Rosenthal, A. (1996). Nature *382*, 76–79.

Pichel, J.G., Shen, L., Sheng, H.Z., Granholm, A.-C., Drago, J., Grinberg, A., Lee, E.J., Huang, S.P., Saarma, M., Hoffer, B.J., et al. (1996). Nature *382*, 73–76.

Rossi, J., Luukko, K., Poteryaev, D., Laurikainen, A., Sun, Y.F., Laakso, T., Eerikàinen, S., Tuominen, R., Lakso, M., Rauvala, H., et al. (1999). Neuron *22*, this issue, 243–252.

Sánchez, M.P., Siols-Santiago, I., Frisén, J., He, B., Lira, S.A., and Barbacid, M. (1996). Nature *382*, 70–73.

Schuchardt, A., D'Agati, V., Larsson-Blomberg, L., Costantini, F., and Pachnis, V. (1994). Nature *367*, 380–383.

Drosophila Odor Receptors Revealed

Drosophila melanogaster is an attractive model system for gaining insights into olfactory function, organization, and development. Insect chemosensory systems have many parallels with vertebrate olfactory systems. In both cases, for example, primary olfactory neurons project directly to the central nervous system, where they synapse in discrete neuronal clusters called glomeruli (reviewed by Hildebrand and Shepherd, 1997). Odorants elicit distinct, reproducible patterns of activity in different glomeruli in both insects and vertebrates, suggesting that odors are represented by specific glomerular activity patterns. *Drosophila* have ~40 glomeruli, compared to 1800–2000 for a typical vertebrate, so understanding the relationship between odor sensitivity of olfactory neurons and their glomerular innervation, and ultimately with olfactory behavior, should be approachable in this system. However, progress toward these goals has been hampered by the lack of molecular probes to identify functional sets of olfactory neurons. Specifically, the transmembrane receptors mediating odor responses in insects have eluded cloning efforts. Now, two groups (Clyne et al., 1999 [this issue of *Neuron*]; Vosshall et al., 1999 [5 March issue of *Cell*]) report the identification of a family of genes encoding seven-transmembrane proteins likely to function as *Drosophila* odor receptors. These genes have no sequence similarity to either *C. elegans* or vertebrate chemoreceptor families and constitute a novel branch of the G protein–coupled receptor family.

Clyne et al. (1999) and Vosshall et al. (1999) used different strategies to identify candidate receptor genes. Using a novel, multivariable computer algorithm to search the *Drosophila* genome database, Clyne et al. identified candidate genes and used reverse transcription with polymerase chain reaction (RT–PCR) to identify two genes from their candidates that were expressed exclusively in the chemosensory organs. Blast searches of the genome database using these chemosensory-specific receptor candidates ultimately resulted in the identification of 16 genes.

Vosshall et al. (1999) used a molecular approach to identify genes expressed at low levels in the chemosensory organs. They picked 5000 plaques from a chemosensory organ library that failed to hybridize with genes expressed in *Drosophila* bodies or with abundantly expressed antenna-specific genes. They then sequenced all clones that failed to hybridize in a second round of hybridization to body cDNA and to cDNA from heads lacking chemosensory organs. One clone encoded a putative seven-transmembrane protein expressed in a small subset of chemosensory neurons. This sequence was used in homology searches to identify additional receptor genes, resulting in the identification of most of the same genes identified by Clyne et al. (1999). Between the two groups, a total of 17 genes have been identified.

Several features of this new putative receptor family are worth noting. First, these receptors are members of a highly divergent family. The *Drosophila* proteins share no significant homology to any other G protein–coupled receptor family and share strikingly little homology among themselves. Given the lack of success in isolating these genes with homology-based approaches, the low sequence similarity with other odor receptor families was not unexpected. Nonetheless, it is a puzzle why vertebrates, flies, and worms share so little sequence similarity in this receptor family.

Second, the *Drosophila* genome project has completed roughly 15% of the genome, suggesting that a total of 100–200 members of this family are likely to be present in the genome. However, this estimate might be low, as the 17 receptors identified so far appear to be expressed only in one of the three major morphological classes of sensillum. Therefore additional, distantly related genes may be uncovered by further sequencing.

The third noteworthy feature of the receptor family is that the spatial expression patterns of the putative receptor genes indicate that each receptor is expressed in a stereotypical pattern of neurons that is similar or identical across individuals (Vosshall et al., 1999). This is distinct from vertebrates, in which olfactory neurons expressing particular receptors are randomly distributed within particular expression zones.

Finally, so far, multiple *Drosophila* receptor genes appear not to be coexpressed in the same olfactory neurons, which suggests that individual olfactory neurons express one or a small number of receptor genes. In this regard, the organization of the *Drosophila* chemosensory system is more reminiscent of vertebrates, in which one or a small number of receptors is expressed per neuron, than of *C. elegans*, in which large numbers of receptor genes are expressed in individual neurons. A final determination of how many receptors are expressed in single *Drosophila* olfactory neurons must await a more complete analysis of the expression patterns of additional receptor genes. However, if there are 1200 primary chemosensory neurons that each express 1 of 100 receptor genes, there should be ~12 cells expressing any particular receptor. This is similar to the numbers actually observed (Clyne et al., 1999; Vosshall et al., 1999).

It will be interesting to establish the relationship between the expression of odorant binding proteins (OBPs) and the neuronal receptors. In *Drosophila*, OBPs are abundant, low molecular weight proteins secreted into the fluid within the sensilla that bathes the olfactory neuron dendrites. Invertebrate OBPs are a distinct family of proteins unrelated to the vertebrate lipocalin OBP

members (Pelosi, 1994). Individual OBP genes are expressed in fixed, overlapping zones on the surface of the antenna in *Drosophila*, and expression patterns often correlate with specific classes of sensilla. While the biochemical role of these proteins has not yet been established, mutations in one *Drosophila* OBP, LUSH, clearly demonstrate a function in odor discrimination (Kim et al., 1998), perhaps by differentially concentrating specific odors in specific sensilla.

Vertebrate odor receptors play an important role in axonal targeting to a particular glomerulus (Mombaerts et al., 1996; Wang et al., 1998). Clyne et al. note that at least one *Drosophila* receptor is expressed early in development at a time when neurons are still invading the antenna lobes. This finding raises the possibility that the *Drosophila* receptors may participate in establishing the olfactory neuron circuitry.

In a second manuscript in this issue of *Neuron*, Clyne et al. (1999) report that Acj6, a mutant with abnormal chemosensory behavior, results from deletions in a POU-homeodomain transcription factor. Other members of this family of transcriptional regulators mediate the terminal differentiation of a variety of sensory cells in vertebrates, including retinal ganglion cells and auditory hair cells (reviewed by Ryan and Rosenfeld, 1997). Interestingly, Acj6 mutants are specifically defective for expression of a subset of the new receptor genes. Electrophysiological analysis of wild-type and Acj6 mutants reveals that a specific subset of olfactory neurons have altered chemical specificity in Acj6 mutants. Two groups of neurons in Acj6 appear to have lost all odor sensitivity, while a third population has acquired a unique odor response profile not found normally.

We do not have enough information to explain these results at a mechanistic level, but at least three broad possibilities emerge. A subset of receptors in Acj6 may simply be lost, leaving behind either no receptors, nonfunctional receptors, or a novel combination of receptors not normally expressed in the wild type. A single receptor may be ectopically expressed in those Acj6 olfactory receptor neurons with unique response profiles. Or, alternatively, the defects in Acj6 may reflect an alteration in cell fate or terminal differentiation of a subset of olfactory neurons or a complex interaction between transcription factors required for proper expression of signaling components. Further insights await a more detailed analysis of the changes in receptor expression in Acj6 mutants compared to wild type.

Together, these studies mark the beginning of a new era in insect chemosensory research. The availability of these receptors will usher in a period of rapid advancement in our understanding of the molecular details of chemosensory function, structure, and development in *Drosophila*. These findings should translate into insights into chemosensory function in other arthropods (including pests) and more complex olfactory systems like our own.

Dean P. Smith
Department of Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas 75235

Selected Reading

Clyne, P.J., Warr, C.G., Freeman, M.R., Lessing, D., Kim, J., and Carlson, J.R. (1999). Neuron *22*, this issue, 327–338.

Clyne, P.J., Certel, S., de Bruyne, M., Zaslavsky, L., Johnson, W., and Carlson, J.R. (1999). Neuron *22*, this issue, 339–347.

Hildebrand, J.G., and Shepherd, G.M. (1997). Annu. Rev. Neurosci. *20*, 595–631.

Kim, M.-S., Repp, A., and Smith, D.P. (1998). Genetics *150*, 711–721.

Mombaerts, P., Wang, F., Dulac, C., Chao, S.K., Nemes, A., Mendelsohn, M., Edmondson, J., and Axel, R. (1996). Cell *87*, 675–686.

Pelosi, P. (1994). Crit. Rev. Biochem. Mol. Biol. *29*, 199–228.

Ryan, A.K., and Rosenfeld, M.G. (1997). Genes Dev. *11*, 1207–1225.

Vosshall, L.B., Amrein, H., Morozov, P.S., Rzhetsky, A., and Axel, R. (1999). Cell *96*, in press.

Wang, F., Nemes, A., Mendelsohn, M., and Axel, R. (1998). Cell *93*, 47–60.

A Sweet Beginning

Animals have developed highly specialized sensory organs that detect physicochemical characteristics in the environment and translate this information into neuronal electrical activity. The coding of sensory stimuli into specific patterns of neuronal activity generates an internal representation of the external world that is processed by brain centers to elicit complex sensory perception and adapted behavioral responses. Major advances in the study of olfaction have resulted from the identification of genes encoding olfactory receptor molecules (see, for example, Buck and Axel, 1991; Buck, 1996). Similarly, the recent characterization of novel genes encoding taste receptors will undoubtedly shed a new light on the logic of taste sensory processing.

The sense of taste provides the animal with an immediate perception of food palatability: the hedonic perception of sweet, for example, signals highly caloric carbohydrate-rich nutrients, whereas potentially toxic substances such as plant alkaloids or cyanides elicit aversive bitterness. The initial event of taste recognition requires the activation of specific populations of taste receptor cells by tastant molecules. In mammals, onion-shaped clusters of taste receptor cells, the taste buds, are distributed within the different papillae of the tongue epithelium (see figure). Taste cells synapse with afferent nerve fibers connected to the gustatory nuclei in the brainstem, which in turn transmit sensory information to limbic and cortical brain areas. How are the diversity and specificity of the taste sensory response accomplished? Only five distinct gustatory perceptions have been identified in mammals: sweet, bitter, sour, salty, and umami (monosodium glutamate) (Linderman, 1996). Psychophysical studies have identified a coarse topographic organization of taste buds in distinct areas of the tongue according to preferential gustatory sensitivity (see figure). To a certain extent, however, all tastants can be detected throughout the tongue. In addition, although taste receptor cells are selectively activated by various tastants, individual taste cells and taste fibers are usually broadly tuned, showing sensory responses to several chemical stimuli (Frank, 1973). A simple model